Journal of the American College of Cardiology Vol. 46, No. 10, 2005

Published by Elsevier Inc.
ISSN 0735-1097/05/$30.00
doi:10.1016/j.jacc.2005.07.032

EDITORIAL COMMENT

At the Heart of the Statin Benefit*

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Almost since they were first introduced, statin drugs have been recognized to have effects beyond their potent low-density lipoprotein (LDL)-lowering abilities. These "pleitropic" effects include anti-inflammatory, vascular, and immune-altering properties (1). Their existence has led to suggestions that statins might be useful in other diseases, ranging from dementia to autoimmune disorders. They have been invoked to explain the unexpectedly early reduction in coronary events in statin clinical trials, contrary to the later appearance of benefits in non-statin LDL-lowering trials. They also have been implicated in the strong benefit of statin therapy in preventing atherothrombotic strokes, even though cholesterol levels are, at best, weak predictors of stroke in observational studies. Evidence of the prominent role of inflammation in atherogenesis has grown apace with the evidence for the anti-inflammatory effects of statins. Perhaps as a result, this property has received the most attention as one of potential clinical significance.

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On the other hand, it has been evident for some time that average achieved LDL cholesterol levels in placebo and treatment groups in various statin trials, when plotted against coronary event rates, depict a remarkably linear relationship. In other words, the results of studies in different populations (all with stable, not acute coronary disease), using different statins, at different times, reveal a linear relationship that fully accounts for the decline in event rates, without the need to invoke other mechanisms (2).

The "meta-regression" study by Robinson et al. (3) in this issue of the *Journal* refines and extends these observations. By demonstrating that LDL lowering in non-statin trials bears the same relationship to event rates as is found in statin trials, this analysis adds strong support to the hypothesis that LDL decline is sufficient to explain the observed benefits without invoking pleitropic effects.

The clinical trials selected for comparison in this analysis were all performed in patients with stable coronary disease. Statin trials involving patients with acute coronary syndromes were not included. As a result it is not possible to say whether anti-inflammatory pleitropic effects might play a more prominent role in patients with acute coronary syndromes, in whom more active and inflamed plaque might be present.

Interestingly, overall stroke reduction also appears to be accounted for primarily by LDL cholesterol reduction, although the absence of stroke end points in non-statin trials limits this conclusion.

How should these findings shape our thinking? First, none of these results imply that pleitropic effects are nonexistent. A wealth of laboratory and translational research exists describing and confirming these effects of statin. In some cases, these effects appear to be wholly independent of any changes in circulating lipid fractions. What is at issue in not the existence of pleitropic effects but their clinical significance in the prevention of vascular events. In many ways, this situation is comparable with that of estrogen, where many well-described benefits on vascular function have not translated into clinical benefits in trials (4,5).

The analysis by Robinson et al. (3) strongly supports the concept that declines in coronary and probably cerebrovascular events in patients with stable atherosclerosis result largely from declines in LDL levels. It does not appear, moreover, that the means by which LDL is lowered is of significant.

Pleitropic effects are of great scientific interest and may point to the mechanisms of statin benefits in disorders completely unrelated to circulating lipids. However, the burden of proof that they are of clinical consequence in atherosclerosis has not been met. At this point, the benefits of statins and other lipid-altering regimens appear to be operating chiefly through LDL lowering. As a result, agents that can most effectively and safely achieve the lowest LDLs are likely to be the most useful in preventing recurring coronary events.

Whether the same might be said for raising high-density lipid protein, lowering triglyceride, diminishing inflammation, or altering vascular dysfunction independent of LDL lowering is not yet firmly established. While we look for other interventions to extend the reductions in the catastrophic results of atherosclerosis, however, we should not fail to apply the one intervention that has now been proven beyond a reasonable doubt, i.e., aggressive and sustained lowering of LDL cholesterol.

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From the SUNY Downstate Medical Center, Brooklyn, New York. Dr. LaRosa is a consultant for Pfizer, Bristol-Myers, and Merck but is not employed by any of them, has no research grants from any of them, and owns no stock in any of them.